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ARTICLE

Evaluation of the effect of erenumab on migraine-specific questionnaire in patients with chronic and episodic migraine

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Abstract

Erenumab is a fully human anti-canonical calcitonin gene-related peptide receptor monoclonal antibody approved for migraine prevention. The Migraine-Specific Quality-of-Life Questionnaire (MSQ) is a 14-item patient-reported outcome instrument that measures the impact of migraine on health-related quality of life. Erenumab data from four phase II/III clinical trials were used to develop an item response theory (IRT) model within a nonlinear mixed effects framework, (i) evaluate the MSQ item information with respect to patient disability, (ii) characterize the longitudinal progression of the MSQ, and (iii) quantify the effect of erenumab on the MSQ in patients with migraine. The majority (80%) of information was found to be contained in 9 out of 14 items, extending the current knowledge on the reliability of the MSQ as a psychometric tool. Simulations across three MSQ domains show significant improvement from baseline, exceeding minimally important differences. Overall, the IRT model platform developed herein allows for systematic quantification of the effect of erenumab on the MSQ in patients with migraine.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Erenumab is a fully human anti-canonical calcitonin gene-related peptide receptor monoclonal antibody approved for migraine prevention. There is a lack of a comprehensive quantitative approach that systematically evaluates the effect of erenumab on the Migraine-Specific Quality-of-Life Questionnaire (MSQ).

WHAT QUESTION DID THIS STUDY ADDRESS?

This analysis (1) evaluated the reliability of MSQ as psychometric tool that measures the impact of migraine, (2) characterized the longitudinal progression of

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disease using the MSQ in patients with migraine, and (3) quantified the effect of erenumab on MSQ in patients with migraine.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This model-based analysis indicates that the MSQ is a robust and sensitive psychometric tool that can be used to reliably measure the impact of erenumab treatment on migraine. This platform item response theory (IRT) model adequately captures both the longitudinal progression of disease using the MSQ in patients with migraine and an array of diverse treatment benefits observed in the migraine population receiving erenumab.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

A platform IRT model approach could be used to systematically quantify the effect of erenumab and other migraine medications in chronic migraine and episodic migraine using the MSQ as a psychometric instrument.

INTRODUCTION

Migraine is a disabling neurologic disorder that can impair daily activity and physical function. Symptoms associated with migraine are decreased patient health-related quality of life (HRQOL), social and psychological impact, and increased disability.[1] Depending on the number of migraine days and headache days per month, migraine can be classified as either episodic migraine (EM) or chronic migraine (CM).[2] EM accounts for more than 90% of migraine cases[2] and are defined as fewer than 15 migraine days or headache days per month, with or without aura. CM, defined as at least 15 headache days per month for more than 3 months (of which ≥8 are migraine days with or without aura), affects ~5% to 8% of patients with migraine.[3] The Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ)[4-6] is a 14-item Patient Reported Outcome (PRO) instrument that measures the impact of migraine across three essential aspects of a patient's HRQOL over the past 4 weeks: (1) role function-restrictive (MSQ-RFR), (2) role function-preventive (MSQ-RFP), and (3) emotional function (MSQ-EF).[5,7] Evidence assessing the reliability and validity of MSQ for migraine has been extensively investigated.[5] Validation and reliability of MSQ in migraine is reported in refs. 5,8, and 9. The minimal important difference (MID)[7] is a metric commonly used to assess the significance of changes in score in quality of life instruments. Cole et al.[7] showed that the threshold value MID for MSQ-RFR is 3.2, for MSQ-RFP is 4.6, and for MSQ-EF is 7.5.

Erenumab (erenumab-aooe, in the United States) is a fully human anti-canonical calcitonin gene-related peptide receptor monoclonal antibody approved for migraine prevention. The efficacy and safety of erenumab among patients with EM and CM have been extensively evaluated.[10–20] In phase ii studies, the safety and efficacy of erenumab for preventive treatment of CM and EM have been reported by Sun et al.[11] and Tepper et al.[12] In both analyses, erenumab was found to significantly reduce the number of migraine days per month in patients with EM at a monthly dose of 70 mg[11] and in patients with CM at doses of 70 and 140 mg.[12] In STRIVE (NCT02456740), erenumab was found to significantly reduce the number of monthly migraine days and monthly acute migraine-specific medication days compared with placebo.[14] The long-term efficacy and safety of erenumab in patients with EM has been evaluated in the LIBERTY study,[16] and in a 5-year open-label study (NCT01952574).[17] Erenumab was found to result in sustained efficacy through 64 weeks and its safety was consistent with that observed in previous clinical trials. MSQ was evaluated by Lipton et al.[15] in a double-blind, placebo-controlled study in 667 adults with CM who were randomized (3:2:2) to placebo or erenumab (70 or 140 mg monthly). The least-squares mean change from baseline was used to assess MID in MSQ across different domains. The analysis found all three MSQ domains were improved from baseline with treatment differences for both doses exceeding MID established for MSQ-RFR (≥3.2) and MSQ-EF (≥7.5) and for MSQ-RFP (≥4.5) for erenumab 70s and 140 mg except for MSQ-RFP with the 70 mg group. Buse et al.[13] evaluated the effect of erenumab on MSQ for patients with EM enrolled in a phase III, 6-month, double-blind, placebo-controlled study of once-monthly erenumab 70 and 140 mg for migraine prevention (STRIVE). A generalized linear mixed-effects model was used to describe the least-squares mean MSQ responses at each monthly timepoint and the mean over months 4–6 of treatment. The between-group differences

from placebo over months 4–6 for erenumab 70s and 140 mg, respectively, were 5.1 and 6.5 for MSQ-RFR, 4.2 and 5.4 for MSQ-RFP, and 5.2 and 6.7 for MSQ-EF. Both statistical methods used by Buse et al.[13] and Lipton et al.[15] analyzed the total score, ignoring the contribution of each questionnaire item to the disease state.

During recent years, modern psychometric methods, such as the item response theory (IRT), have emerged as relevant modeling approaches for analyzing standardized health status questionnaires.[21–29] Within the migraine therapeutic area, IRT is mostly used to evaluate properties of PRO end points using cross-sectional data. Kawata et al. used IRT to successfully evaluate the robustness of the psychometric properties of the Migraine Functional Impact Questionnaire[23] and the Migraine Physical Function Impact Diary,[24] while Bjorner et al.[25] used IRT to evaluate the psychometric properties of MSQ. Recently, IRT within a pharmacometric framework,[26–28] has been used to described the longitudinal nature of clinical end points related to health status questionnaires, and permitted the evaluation of covariates, drug exposure, and clinical end points. To the best of our knowledge, there has not been application of pharmacometric- IRT that systematically evaluated the effect of erenumab on MSQ in patients with CM and EM. Here, we report the development of a pharmacometric IRT platform model that (1) evaluates MSQ item information with respect to patient disability, (2) characterizes the longitudinal progression of MSQ in patients with migraine, and (3) quantifies the effect of erenumab on MSQ in patients with migraine.

METHODS

MSQ version 2.1 was used in this analysis which is a self-administered 14-item instrument assessment of quality of life developed to assess the effect of migraine on daily functioning across three domains: (1) role function-restrictive (MSQ-RFR) domain composed of seven items measuring the effect of migraine on daily social and work-related activities, (2) role function-preventive (MSQ-RFP) domain composed of four items that assesses whether migraine prevents the individual from performing work-related activities, and (3) emotional function (MSQ-EF) domain composed of three items measuring emotions associated with migraine. Each MSQ questionnaire is comprised of a six-point scale: "none of the time," "a little bit of the time," "some of the time," "a good bit of the time," "most of the time," and "all of the time," that are assigned scores of 1 to 6, respectively.[8,9] Table S1 presents a detailed list of questionnaires. In all studies considered in this analysis, patients reported their MSQ score using electronic diaries that contain additional information on migraine status (e.g., incidence of headache, time of onset of headache, time of resolution of headache, pain severity per headache, etc.). For each study visit, the MSQ was completed prior to invasive procedures (e.g., blood draws).

The pooled analysis dataset is composed of four clinical studies from phase II and phase III including both patients with EM and CM.[11,12,14,20] Only patients receiving placebo, patients receiving 70 mg erenumab, and patients receiving 140 mg erenumab in double-blind treatment phase were considered in this analysis. Further details of the four studies are included in Table S2. All patients from clinical studies considered in this analysis provided written informed consent and studies were conducted in accordance with the protocol, good clinical practice standards, and the Declaration of Helsinki. All protocols and amendments were approved by the appropriate institutional review board or ethics committee at each participating institution.

Item response theory modeling

The IRT modeling approach used in this analysis was drawn from previously published work by Ueckert.[26,27] In this approach, the individual MSQ items were related to a latent "unobserved IRT disability" variable through "item characteristic functions" from which their parameters were estimated using baseline MSQ data and item characteristic curves (ICCs) were used for their visualization. In the second step, longitudinal progression of the MSQ for patient i was predicted by developing a disease progression model for the latent variable of patient i (unobserved IRT disability of patient i), $\psi_i(t)$, using MSQ longitudinal data and fixing all parameters of the IRT model from their previously estimated values. Following this approach, the probability for patient i to achieve at least a response k at item j was modeled using an ordered categorical model:

$$P\left(Y_{ij} \geq k\right) = \frac{e^{a_j\left(\psi_i(t) - b_{jk}\right)}}{1 + e^{a_j\left(\psi_i(t) - b_{jk}\right)}}$$

and the cumulative probability for a score of D categories to achieve exactly k was modeled as:

$$P\left(Y_{ij} = 0\right) = 1 - P\left(Y_{ij} \geq 1\right)$$

$$P\left(Y_{ij} = k\right) = P\left(Y_{ij} \geq k\right) - \left(Y_{ij} \geq k + 1\right)$$

$$P\left(Y_{ij} = D\right) = P\left(Y_{ij} \geq D\right)$$

where, Y_{ij} is the patient i observed response to j^{th} item with a response of at least k, a_j is the item-specific discrimination parameter, and b_{jk} is the difficulty parameter, representing

the disability at which there is a 50% probability of obtaining a positive response for that item. Parameters a_j and b_{jk} were modeled as fixed effects and estimated using baseline MSQ data. The patient's time-dependent latent variable value $\psi_i(t)$ was modeled as patient-specific random effect and assumed to follow a standard normal distribution on an arbitrary scale (from $-\infty$ to $+\infty$).[26,27]

Predicting longitudinal progression of MSQ

The longitudinal progression of MSQ following erenumab treatment was quantified by the evolution of the latent variable $\psi(t)$ over time that was predicted in three steps (1) development of the progression of latent variable $\psi(t)$ over time using placebo data; (2) development of $\psi(t)$ over time for patients with migraine on erenumab treatment; and (3) assessment of relevant covariates influencing the longitudinal progression of the latent variable $\psi(t)$ over time. Potential covariates were tested for inclusion in the model using the stepwise covariate modeling function of PsN,[30,31] which involves testing of covariate relationships in a forward inclusion (reduction in the objective function value [ΔOFV] of 6.63; $p < 0.01$ for 1 degree of freedom) and the backward exclusion (ΔOFV of 10.8; $p < 0.001$ for 1 degree of freedom) procedure.

Model implementation and validation

Nonlinear mixed-effects modeling implemented in NONMEM[32] was used to develop the pharmacometric IRT framework. Pearl Speaks NONMEM (https://uupharmacometrics.github.io/PsN/),[33,34] R software (www.r-project.org),[35] Xpose4 (http://xpose.sourceforge.net)[36] were used for the exploratory analysis and postprocessing of NONMEM output. The Piraid IRT model assembler and diagnostics R package[37] was used to alleviate the complexity related to the pharmacometric IRT model development. The first-order conditional estimation method with Laplace approximation (LAPLACE) was used for optimization. Parameter plausibility and the OFV were used as the metric for model selection. The selection of a more complex model was based on the likelihood ratio for nested models, while the Akaike information criterion was used for non-nested models. The fit obtained based on the model-predicted estimates of ICCs for each item were validated by comparing their estimates from a generalized additive model (GAM) using a cross-validated cubic spline as a smoothing function in R.[38] Visual predictive check plots (VPCs) from which 2.5th, 50th, and 97.5th percentiles of the observed data were compared to the 95% confidence interval (CI) for the 2.5th, 50th, and 97.5th percentiles of the simulated ($N = 1000$) data were used to visualize the predictive performance of the model.

Assessment of information content

One of the objectives of this work was to evaluate MSQ item's information with respect to patient disability, as this could be used to optimize the selection of the most informative subset of items in everyday clinical practice. The Fisher information was used as a metric to quantify the item information content as it was directly linked to the expected variance of the individual latent variable estimates. For each MSQ item j, the Fisher information was calculated as the negative expectation of the second derivative of the log-likelihood. The population information was defined as the Fisher information integrated over the entire disability range.[26] The resulting information values were ranked for each item and visualized to illustrate the sensitivity of each assessment item over the full disability range. Items that collectively contain 80% of the information were defined as the most informative.

Simulation

Simulations were performed across MSQ subdomains to determine the effect of erenumab treatment. Stochastic Monte Carlo simulations including parameter uncertainty from the estimated asymptotic variance–covariance matrix of the IRT model parameters were used to generate the MSQ profiles for 3 months for 1000 virtual patients across each MSQ subdomain. Subsequently, the longitudinal latent variable associated with each virtual patient was back-transformed using the item characteristic functions to obtain the normal scale MSQ profile. The MSQ profiles for each subdomain were calculated for the erenumab treated groups and placebo. The obtained MSQ profile across the three subdomains together with their CI were compared with MID reference values reported by Cole et al.[7] For patients with CM, the predicted values of MID were compared with literature values reported by Lipton et al.[15]

RESULTS

The final analysis dataset was composed of 2440 patients of whom 1041 (42.7%) received placebo, and 892 (36.6%) and 507 (20.8%) received 70 and 140 mg doses of erenumab, respectively. Most patients in the analysis dataset were women (2053, 84.1%) and most were White (2219,

TABLE 1 Patients disposition in the analysis dataset.

Clinical studies	STD1	STD2	STD3	STD4	Total
Dosing regimens					
Placebo, *n*	153 (59.1%)	282 (42.7%)	318 (33.5%)	288 (50.4%)	1041 (42.7%)
70 mg, *n*	106 (40.9%)	190 (28.8%)	313 (32.9%)	283 (49.6%)	892 (36.6%)
140 mg, *n*	NA	188 (28.5%)	319 (33.6%)	NA	507 (20.8%)
Demographics					
Sex: female, *n*	207 (79.9%)	549 (83.2%)	811 (85.4%)	486 (85.1%)	2053 (84.1%)
Sex: male, *n*	52 (20.1%)	111 (16.8%)	139 (14.6%)	85 (14.9%)	387 (15.9%)
Age, years	42.0 (9.99)	42.1 (11.3)	40.9 (11.2)	42.3 (11.4)	41.7 (11.2)
Race: White, *n*	238 (91.9%)	621 (94.1%)	846 (89.1%)	514 (90.0%)	2219 (90.9%)
Race: Black, *n*	14 (5.41%)	27 (4.09%)	66 (6.95%)	50 (8.76%)	157 (6.43%)
Race: others, *n*	7 (2.70%)	12 (1.82%)	38 (4%)	7 (1.23%)	64 (2.62%)
Migraine status					
CM, *n*	0 (0%)	660 (100%)	0 (0%)	0 (0%)	660 (27%)
EM, *n*	259 (100%)	0 (0%)	950 (100%)	571 (100%)	1780 (73%)
Baseline MSQ					
Role function-restrictive	58.1 (17.2)	43.2 (18.2)	57.6 (18.4)	57.4 (17.0)	53.7 (19.0)
Role function-preventive	73.9 (18.0)	60.5 (20.7)	70.5 (20.2)	70.5 (19.6)	68.1 (20.5)
Emotional functioning	71.6 (21.6)	53.2 (25.8)	70.6 (23.9)	70.3 (23.3)	66.0 (25.3)

Note: STD1, STD2, STD3, and STD4 are analysis dataset from NCT01952574, NCT02066415, NCT02456740, and NCT02483585, respectively.

Data represent mean (SD) unless otherwise indicated. Others include Asian.

Abbreviations: CM, chronic migraine; EM, episodic migraine; MSQ, migraine-specific quality-of-life questionnaire; NA, not applicable.

90.9%), followed by Black (157, 6.43%) and other ethnicity (64, 2.62%). More details on patient disposition in the analysis dataset can be found in Table 1. MSQ scores at baseline for STD2 were slightly lower compared to the other studies with scores of ~43.2, 60.5, and 53.2 for MSQ-RFR, MSQ-RFP, and MSQ-EF, respectively, while MSQ scores at baseline for STD1, ST3, and STD4 were similar (see Table 1). Figure S2 presents longitudinal behavior of MSQ score across treatment groups in the analysis dataset. Baseline MSQ scores, which are similar among treatment groups, are reflective of the severe effect of migraine in all studies.

Baseline model

The IRT model consisted of 84 item-specific parameters that were estimated from the analysis dataset. Estimated parameter values a_j and $b_{j,k}$ together with their accuracy (i.e., standard error) of the ICCs are reported in Table S3. Figure 1 presents the goodness of fit of ICCs obtained using sampling-based cross-validated GAM cubic spline smooth.[26,27] Overall, the cross-validated cubic spline GAM smooth confirmed the adequacy of the estimated ICCs for describing the MSQ data. Figure 2 illustrates the predicted ICCs of each MSQ item. Score 1, corresponding to "none of the time," is most frequently observed for healthier patients and its probability drops quickly as the IRT disability increases (i.e., worsening of migraine disease). The probability of observing a score of 6 corresponding with "all of the time" increases as the IRT disability increases (i.e., worsening of migraine disease). Finally, all probability curves for different scores of MSQ items are mostly distinct over a range of IRT disability levels, suggesting that all MSQ items differentiate between scores for a given range of IRT disability.

Figure 3 summarizes results from the calculation of information content. Figure 3a presents the Fisher information content as a function of IRT disability. The shaded area represents the interval of IRT disability that contains 95% of the study population. Our analysis suggests "how often kept from getting as much done" and "how often difficult to perform at work" as items containing most information whereas the items "how often felt like a burden on others" and "how often afraid of letting others down" contains less information. The ranking of items based on information content, as shown in Figure 3b, suggests that 80% of the information (Fisher Information) is contained within nine out of 14 items. The overall results obtained from the prediction of ICCs confirm that the MSQ is a robust psychometric tool that can be used to reliably measure the impact of patients with migraine with sufficient sensitivity.

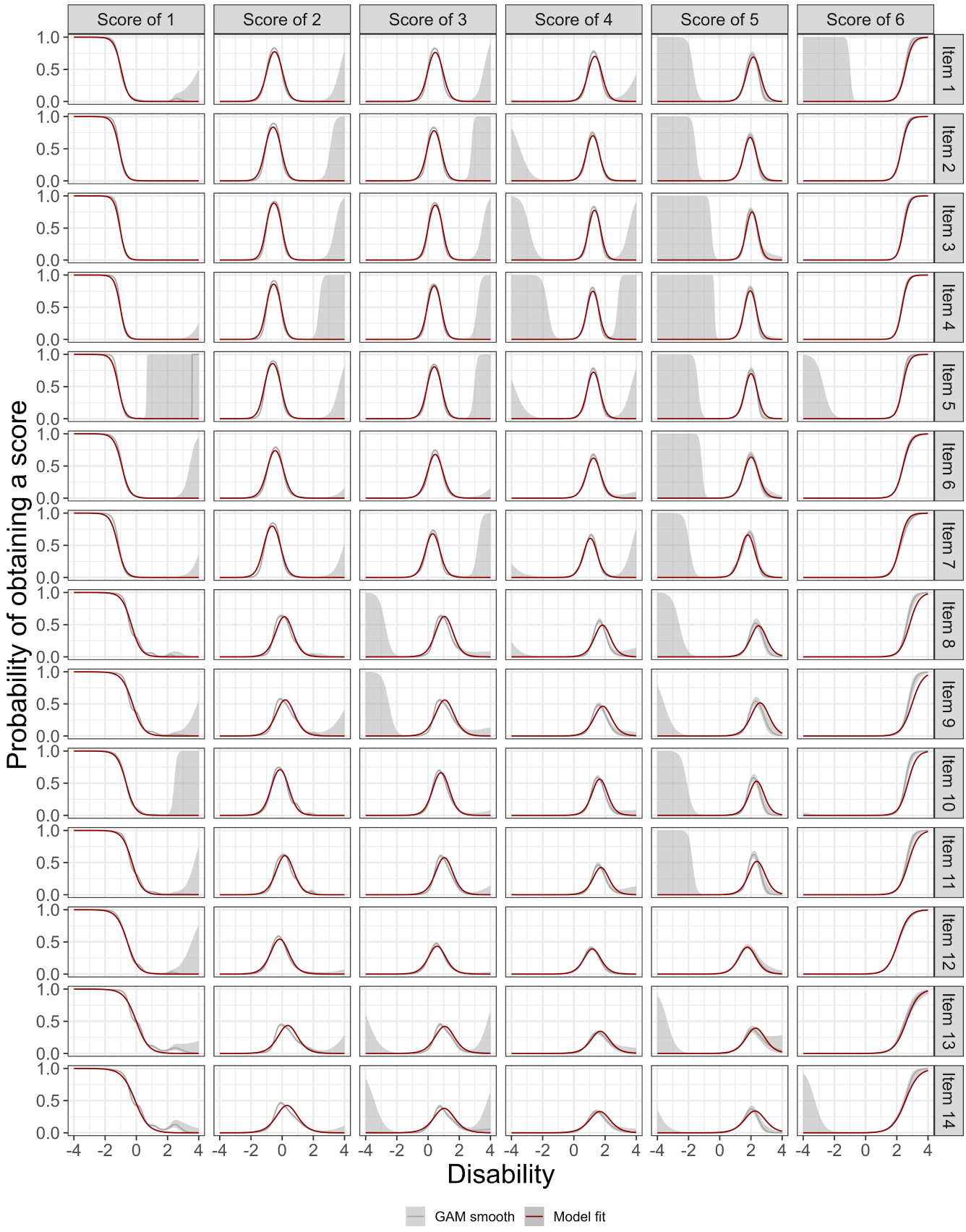


FIGURE 1 MSQ item-level diagnostic comparing the IRT model fit (red line) to the GAM with cross-validated cubic spline as a smoothing function (gray area represent the 95% confidence interval). *X*-axis represents disability of migraine patients, scaled from −4 to 4, where −4 means the best (no disability), and 4 means the worse response (most severe disability). *Y*-axis represents probability of obtaining the score. GAM, generalized additive model; IRT, item response theory; MSQ, Migraine-Specific Quality-of-Life Questionnaire.

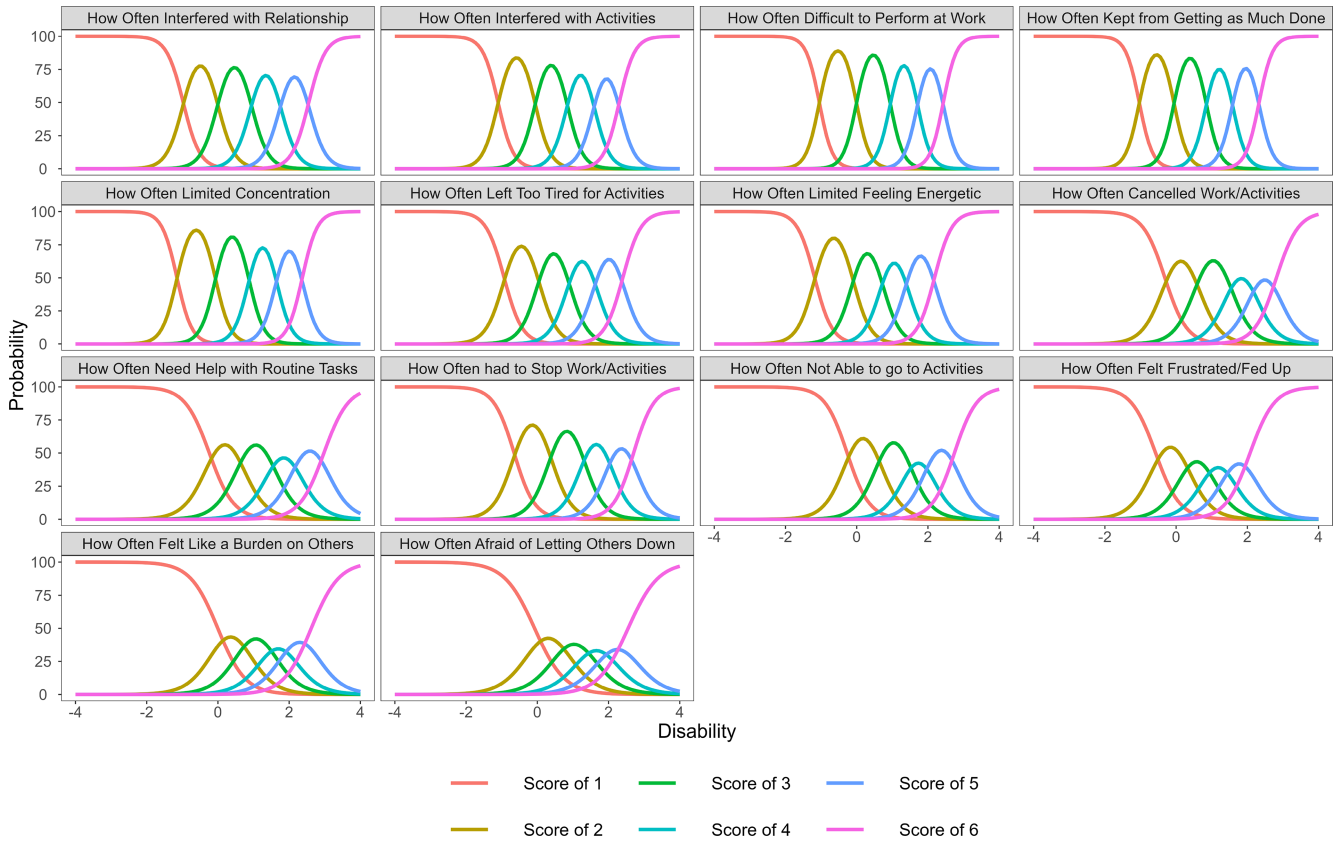
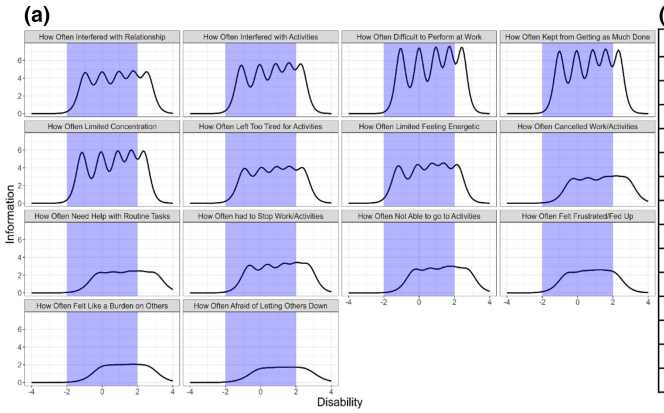


FIGURE 2 Item characteristic curves per item. Colored lines represent probability of occurrence of each score as a function of IRT disability at baseline. Disability (*X*-axis) of patients with migraine is scaled from −4 to 4, where −4 means the best (no disability), and 4 means the worse response (most severe disability). IRT, item response theory.



(b)

MSQ Questionnaire	Information	% Total
How Often Kept from Getting as Much Done?	5.16	11.89
How Often Difficult to Perform at Work?	5.09	11.72
How Often Limited Concentration?	4.38	10.10
How Often Interfered with Activities?	4.31	9.92
How Often Interfered with Relationship?	3.76	8.67
How Often Limited Feeling Energetic?	3.70	8.53
How Often Left Too Tired for Activities?	3.40	7.84
How Often had to Stop Work/Activities?	2.62	6.04
How Often Cancelled Work/Activities?	2.21	5.10
How Often Not Able to go to Activities?	2.14	4.93
How Often Felt Frustrated/Fed Up?	2.09	4.82
How Often Need Help with Routine Tasks?	1.84	4.24
How Often Felt Like a Burden on Others?	1.43	3.29
How Often Afraid of Letting Others Down?	1.26	2.91

FIGURE 3 Information content. (a) Information content for MSQ items versus IRT disability, shaded areas represent disability range of −2 to 2. (b) Ranking of MSQ components by information content in studied population. IRT, item response theory; MSQ, Migraine-Specific Quality-of-Life Questionnaire.

MSQ longitudinal progression model

The identification of the pharmacodynamic models describing the time course of latent variable $\psi(t)$ started by exploring constant the dose-dependent linear model, as described by the equation below:

$$\psi(t) = \text{Baseline} + \text{Slop}(\text{Dose}) * t$$

This model was not able to characterize the nonlinear behavior of $\psi(t)$, as shown in the exploratory plot, see Figure S2. After exploration of several maximum effect type models, the longitudinal progression of MSQ, $\psi(t)$,

in patients receiving erenumab treatment was best represented by a time driven inhibitory-type model described in the equation below:

$$\psi(t) = \text{Baseline} - \frac{f_{T\max}(\text{Dose}) * t}{\left(f_{T50}(\text{Dose}) + t\right)}$$

where $f_{T\max}$ (Dose) and f_{T50}(Dose) are dose-dependent functions and defined as:

- $f_{T\max}(\text{Dose}) = I(x)_{\text{Placebo}} * g^{T\max}_{\text{Placebo}}(\theta,\eta) + I(x)_{70} * g^{T\max}_{70}(\theta,\eta) + I(x)_{140} * g^{T\max}_{140}(\theta,\eta)$
- $f_{T50}(\text{Dose}) = I(x)_{\text{Placebo}} * g^{T50}_{\text{Placebo}}(\theta,\eta) + I(x)_{70} * g^{T50}_{70}(\theta,\eta) + I(x)_{140} * g^{T50}_{140}(\theta,\eta)$

and

- $I(x)_{\text{Dose}} = \begin{cases} 1, & if\ x = \text{Dose} \\ 0, & \text{Otherwise} \end{cases}$

Results from exploratory covariate analysis, as shown in Figure S3, suggested evaluating effects of status (CM or EM) on only baseline and on $f_{T\max}$ (Dose). The final covariate model revealed that migraine status is correlated with both baseline IRT disability and $f_{T\max}$ (Dose). Patients with CM were found to have ~40% higher baseline than patients with EM and ~7% higher drop from baseline than patients with EM. Table 2 shows parameter estimates of the final longitudinal MSQ model. All key parameters were estimated with good precision, as confirmed by the low residual error. The final model was stable upon perturbation of initial parameter estimates and had a low condition number (32.21). There was significant increase of $f_{T\max}$ (Dose) between placebo and patients treated with erenumab. The typical value for placebo (i.e., $f_{T\max}$(Placebo)) was estimated to be 0.681, while the estimated values were 0.886 and 0.957 for $f_{T\max}$ (70 mg) and $f_{T\max}$ (140 mg) , respectively. There was a significant decrease in time to reach 50% of maximum inhibition of MSQ (i.e., f_{T50} (Dose) between placebo and erenumab treatments). The typical value of f_{T50} (Placebo) was estimated to be 4.269, while it was estimated to be 2.661 and 1.972 for f_{T50} (70 mg) and f_{T50} (140 mg), respectively. Both the increase of $f_{T\max}$(Dose) and decrease of f_{T50}(Dose) confirmed the evidence of effectiveness of erenumab on MSQ in all patients considered in the analysis dataset. The VPCs of each item showed good agreement between the observed time-courses of each score and their respective simulated time-courses. The VPCs stratified by erenumab doses are presented in Figure 4. Additional VPCs of each item are presented in Figure S1.

TABLE 2 Population parameter estimate values of the final model and their uncertainty.

Parameters	Latent values (Psi)	Parameter estimates	% RSE
Baseline	All population	0.407	5.478
	Disease state (CM)	1.437	10.610
$f_{T\max}$ (Dose)	Placebo	0.681	5.311
	70 mg	0.886	4.788
	140 mg	0.957	5.559
	Disease state (CM)	0.075	87.16
f_{T50} (Dose)	Placebo	4.269	4.037
	70 mg	2.661	2.893
	140 mg	1.972	5.117
Random effect	IIV on baseline	0.765	1.503
	IIV on T_{max}	1.060	1.686

Abbreviation: CM, chronic migraine; IIV, interindividual variability; Psi, Latent variable; RSE, relative standard errors.

Simulations evaluating the minimally important differences

Figure 5 summarizes the overall predicted effect in patients with CM treated with erenumab across the MSQ subdomains. Figure 5a presents the simulated percentage change from baseline of the MSQ across subdomains in latent variable over time for patients receiving 70 mg, 140 mg erenumab, or placebo. Improvement in the MSQ is predicted at early timepoints (~1 month), and percentage changes from baseline in all MSQ subdomains were consistently greater with 140 mg versus 70 mg and placebo. Furthermore, our simulation results reveal that the subdomain "emotional function" is the more sensitive compared to "role function-prevention" and "role function-restrictive" as it has the highest percentage decrease from baseline. This finding is in agreement with the defined threshold values of MID for the MSQ reported by Cole et al.[7] Based on results shown in Figure 3, the three questions in the "emotional function" subdomain rank among those having the lowest amount of information. A low amount of information per item requires a high number of observations for the precise estimation of item parameters.[26] Figure 5b compares the MID between observed as reported by Lipton et al.[15] and predicted at 3 months for patients with CM receiving 70 mg, 140 mg erenumab, or placebo. The predicted between-group differences at 3 months for patients with CM receiving 70 and 140 mg versus placebo across MSQ subdomains exceeds the established threshold values for MID reported by Cole et al.[7] Specifically, the between group differences at 3 months for

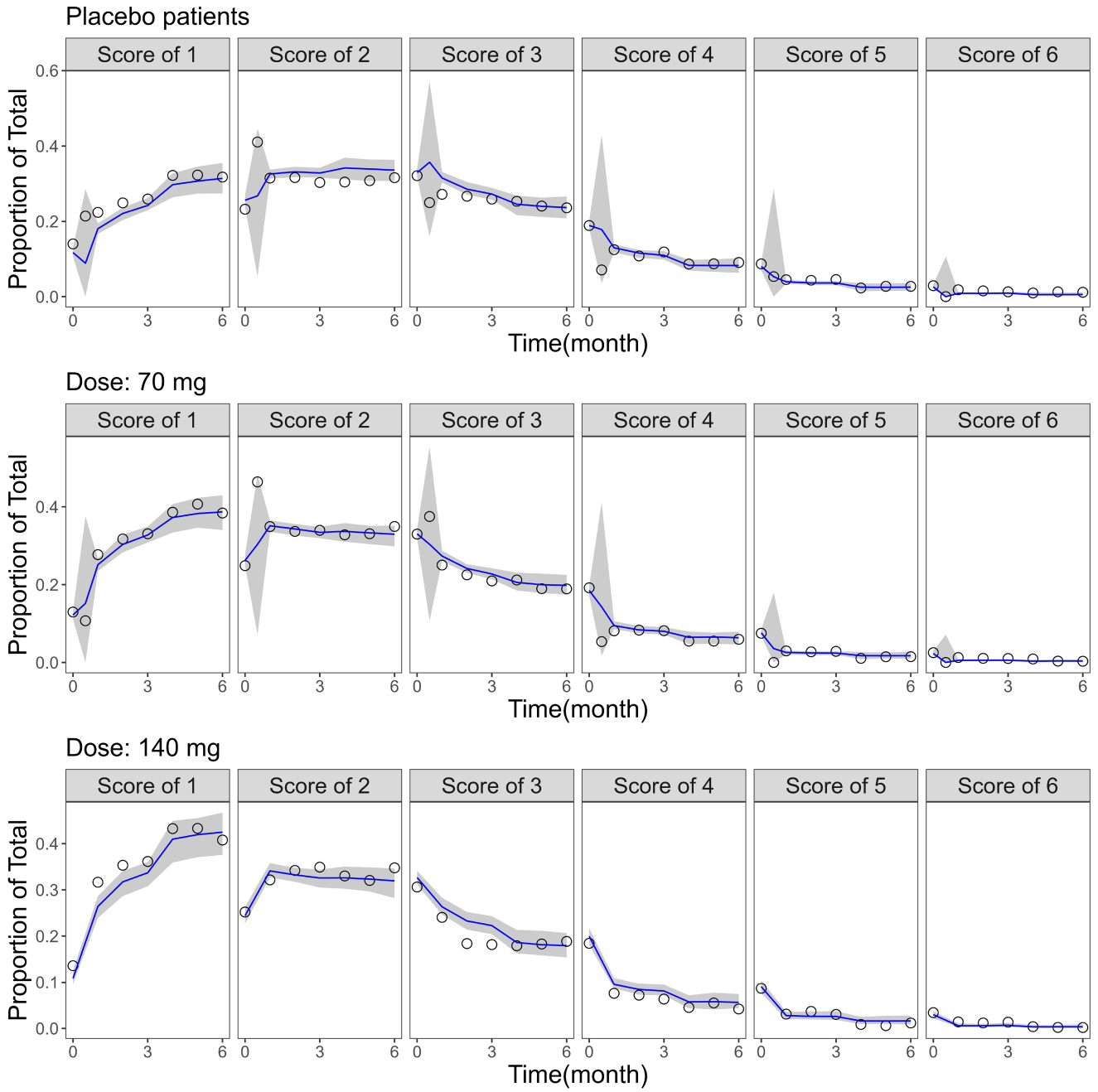


FIGURE 4 Visual predictive checks describing the time-courses of each score stratified by erenumab clinical doses. The *Y*-axis represents the aggregate result for 14 questionnaires in each treatment arm. Symbols represent the median observed data; the blue solid line represents the median model prediction and the shaded area represents the 95% prediction interval of the simulated data.

patients with CM receiving 70 and 140 mg versus placebo were, respectively, 6.25 (4.62, 7.88) and 7.60 (5.96, 9.24) for MSQ-RFR; both exceeding the MID threshold value of 3.2 for this domain.[7] For MSQ-RFP, the between-group differences at 3 months were predicted to be 5.59 (4.08, 7.10) for patients with CM receiving 70 mg and 6.71 (5.19, 8.22) for those receiving 140 mg, both exceeding the MID of 4.6.[7] For MSQ-EF, the predicted between-group differences were 6.20 (4.48, 7.92) for 70 mg and 7.45 (5.73, 9.17) for 140 mg. All predicted error bars representing 95% CIs were smaller than the CIs reported by Lipton et al.[15] confirming the precision of this IRT analysis.

DISCUSSION

Migraine disorder significantly impacts HRQOL and treatments that effectively reduce migraine-associated symptoms are expected to improve patient's HRQOL. The MSQ is a disease-specific PRO metric that has been

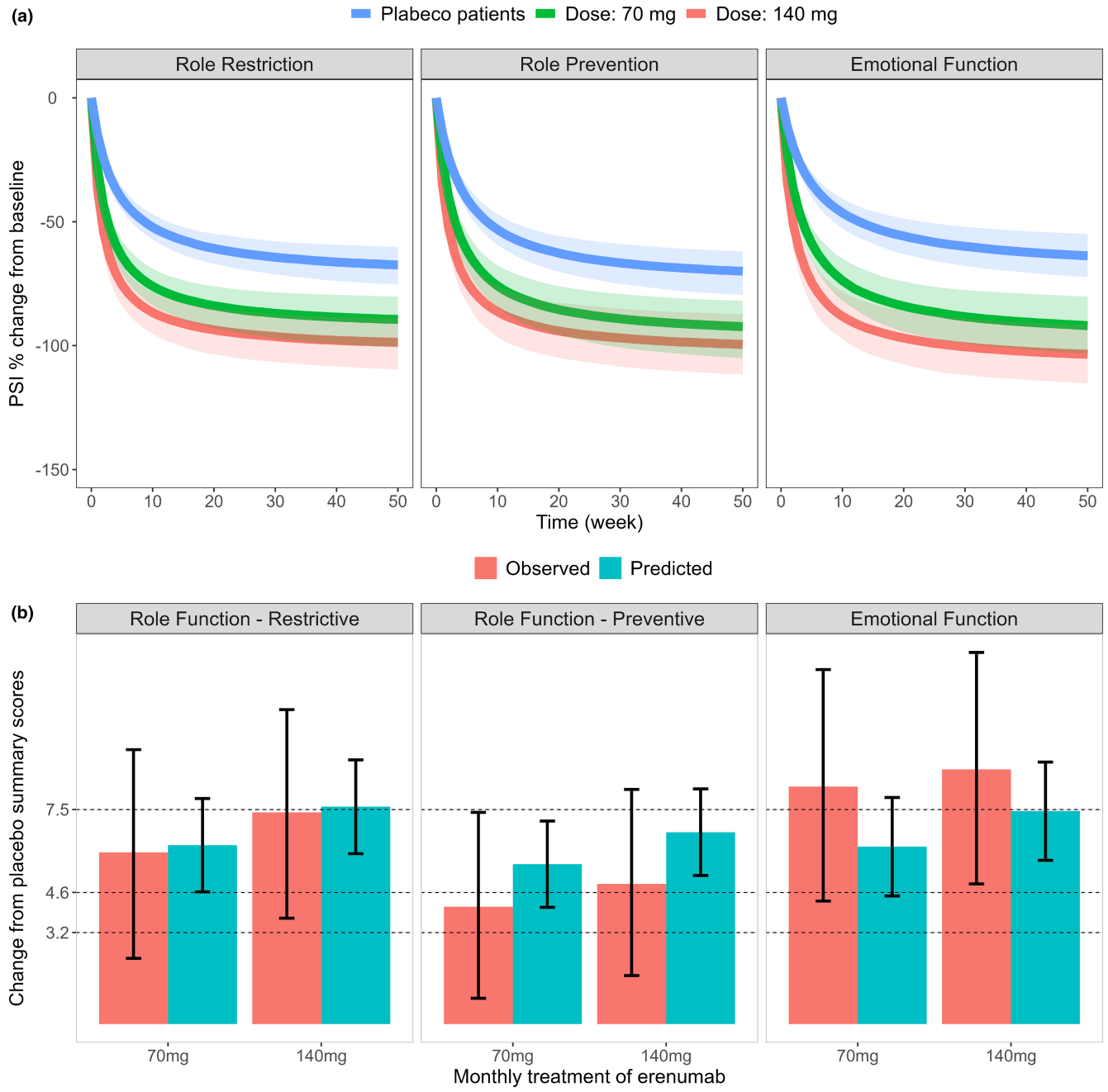


FIGURE 5 Quantifying the effect of erenumab on MSQ. (a) Simulated longitudinal percentage change from baseline MSQ across subdomain in latent scale for patients receiving 70 mg, 140 mg erenumab, or placebo. (b) MID comparison between observed[15] and predicted from current analysis at 3 months for patients with CM receiving 70 mg, 140 mg erenumab, or placebo. The error bars represent 95% confidence intervals. The red bars present results reported by Lipton et al.[15] and the blue bars represent those were obtained from current analysis. CM, chronic migraine; MID, minimal important difference; MSQ, Migraine-Specific Quality-of-Life Questionnaire; PSI, Latent variable.

used to quantify the potential benefits of treatment in migraine clinical trials. Traditionally, the effect of treatment on the MSQ in patients with migraine has been modeled as a continuous variable using a generalized linear mixed-effects model, disregarding the contribution of each item in the questionnaire to the disease state.[13,15] These approaches to analyze questionnaire-based scales generally ignore the categorical nature of the data. A detailed comparison of different approaches to analyze questionnaire-based scales has been performed by Wellhagen et al.[39] Here, the effect of erenumab on MSQ in patients with migraine has been modeled using IRT within a nonlinear mixed effects model framework that accounts for the item level variability of the MSQ. Several diagnostic plots are shown that assess the robustness of all ICCs generated from this work and can be used as

informative priors to analyze future migraine trial data. One of the major contributions of the IRT is the extension of the concept of reliability. Traditionally, reliability is assessed using a single index defined in various ways (e.g., the ratio of true and observed score variance). This index is helpful in characterizing a test's average reliability. However, based on the concept of IRT, it is clear that the precision of the instrument is not uniform across the entire range of test scores.[26] Findings from this analysis extend the MSQ reliability assessment reported by Bagley et al.,[8] Chang et al.,[9] and Martin et al.[5] by clarifying that 80% of the information about underlying disease status, in the studied population, is quantified in nine out of 14 MSQ items.

The second part of this analysis developed a longitudinal IRT model that quantified the effect of placebo/drug on disease progression using MSQ in patients receiving erenumab treatment. Our analysis found that the optimal longitudinal IRT model uses an inhibitory-type time function. To assess the impact of migraine disease status on the final longitudinal IRT model, a stringent significance level was used in testing ($p < 0.01$ in the forward step and $p < 0.001$ in the backward step) to mitigate the likelihood of false positive results given that multiple hypothesis testing is applied during the search.[31] Using these criteria, patients with CM were found to have higher baseline and slightly larger drop from baseline compared to patients with EM. Goodness of fit plots demonstrate the robustness of the final model and provide confidence in simulating several scenarios that quantify erenumab benefits on MSQ.

Lack of efficacy with migraine preventive medication could reduce patient adherence. Our simulations show strong improvements in MSQ scores within 1 month of erenumab treatment, and percentage changes from baseline in all of the MSQ subdomains are greater with 140 mg, consistent with Lipton et al.[15] Buse et al.[13] found that the benefits of treating patients with EM with 70 and 140 mg erenumab, were maintained through 6 months. Specifically, their analysis found the between group differences at 70 and 140 mg versus placebo over months 4–6 exceeded the MID for MSQ-RFR and MSQ-RFP and did not exceed the MID for MSQ-EF. Our simulation of the same protocol deployed by Buse et al.,[13] found that the between-group differences at 70 and 140 mg versus placebo over months 4–6 were, respectively, of 4.86 (3.29, 6.24) and 6.14 (4.59, 7.69) for MSQ-RFR exceeding the MID threshold value of 3.2.[7] For MSQ-RFP, the between-group differences at 70 and 140 mg versus placebo were predicted to be 3.56 (2.25, 4.87) and 4.63 (3.33, 5.92), respectively, exceeding the MID threshold value of 3.2[7] for patients treated with 140 mg. For MSQ-EF, the predicted between group differences at 70 and 140 mg versus placebo were 3.83 (2.39, 5.27) and 4.94 (3.52, 6.36) and did not exceed the threshold value of 7.5 in agreement with findings from Buse et al.[13]

One of the main goals of preventive migraine therapy is to reduce and postpone long-term disability. Traditionally, the effectiveness of migraine therapy on MSQ has been analyzed using cross-sectional data[40] or descriptive statistics using summary scores.[13,15] These methods generally ignore the underlying nature of the data and are not designed to predict the time course of migraine progression, or quantify the role of the individual components of MSQ. The modeling framework developed in this analysis has the ability to address the latter challenges and is designed to predict longtime impact of migraine treatment on MSQ. Furthermore, our platform model is flexible enough to be adapted to analyze data from other PRO instruments commonly used in clinical trials including measures of migraine disability, and HRQOL.

In summary, the approach reported here provides an integrated framework that systematically quantifies the effect of erenumab on the MSQ in patients with CM and EM. The current analysis accounts for the underlying nature and distribution of the data and the effects of explanatory covariates like migraine disease status more thoroughly than those that rely exclusively on separate analysis. The final model captures an array of diverse treatment benefits observed in the migraine population receiving erenumab[13,15] and provides evidence for significant responses to the clinical doses of 70 and 140 mg.

AUTHOR CONTRIBUTIONS

P.-W.C., A.P.-B., M.O.K., S.D., and M.A. wrote the manuscript. M.O.K., S.U., P.-W.C., C.-P.H., S.D., and M.A. designed the research. P.-W.C., S.U., M.O.K., S.D., and M.A. performed the research. P.-W.C., S.U., M.O.K., and M.A. analyzed the data. A.P.-B. and C.-P.H. contributed new reagents/analytical tools.

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CONFLICT OF INTEREST STATEMENT

M.K. and S.U. report personal fees from AMGEN Inc. during the conduct of the study. C.P.H. and M.A. were

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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